(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 461 201 B1**

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication of patent specification: **26.07.95**

(51) Int. Cl.[6]: **A61F 2/38**, A61F 2/28, A61F 2/30, A61F 2/54

(21) Application number: **90905141.9**

(22) Date of filing: **01.03.90**

(86) International application number:
PCT/US90/01141

(87) International publication number:
WO 90/09769 (07.09.90 90/21)

(54) PROSTHETIC MENISCUS.

(30) Priority: **02.03.89 US 317951**

(43) Date of publication of application:
18.12.91 Bulletin 91/51

(45) Publication of the grant of the patent:
26.07.95 Bulletin 95/30

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB IT LI LU NL SE

(56) References cited:
EP-A- 0 277 678
WO-A-88/08305
WO-A-89/00413
GB-A- 1 515 963

BULLOUGH, et al., "The strenght of the Menisci of the knee as it relates to their fine structure". The Journal of Bone & Joint Surgery Vol 52B, No. 3 August 1970, Paragraph 564-570 See page 566.

(73) Proprietor: **REGEN BIOLOGICS, INC.**
3727 Buchanan Street
San Francisco, California 94123 (US)

(72) Inventor: **STONE, Kevin, R.**
133 Retiro Way
San Francisco, CA 94123 (US)

(74) Representative: **Holdcroft, James Gerald, Dr. et al**
Graham Watt & Co.,
Riverhead
Sevenoaks, Kent TN13 2BN (GB)

EP 0 461 201 B1

Description

Field of the Invention

The present invention is in the field of implantable medical devices, and more particularly, is directed to devices useful as prosthetic menisci, and in vivo scaffolds for regeneration of meniscal tissue and to methods for their fabrication.

Background of the Disclosure

The medial and lateral menisci are a pair of cartilaginous structures in the knee joint which together act as a crucial stabilizer, a mechanism for force distribution, and a lubricant in the area of contact between the tibia and femur. Without the menisci, stress concentration occurs in the knee in conjunction with abnormal joint mechanics, and premature development of arthritic changes occurs.

In the prior art, treatment of injured or diseased menisci has generally been both by surgical repair and by excision. With excision, regeneration of meniscal tissue may occur. Additionally, it is known that meniscal fibrochondrocytes have the ability to migrate into a defect filled with a fibrin clot and form tissue apparently similar to normal meniscal fibrocartilage. When an adequate matrix scaffold is present within a meniscal defect, such meniscal fibrocartilage may be formed. Meniscal tissue is also capable of self-repair when exposed to bleeding tissues, and additionally, it is also known in the prior art that meniscal cells in tissue culture are capable of cell division and matrix synthesis. Replacement of an injured meniscus in an otherwise healthy joint may prevent arthritic changes and may stabilize the joint. In diseased joints, replacement of the meniscus may reduce the progression of the disease process, and may provide pain relief. Allografting or meniscal transplantation, is one method of replacement which has been executed both in dogs and in humans. However, this approach has been only partially successful over the long term due to the host's immunologic response to the graft, to failures in the cryopreservation process, and to failures of the attachment sites.

In alternative prior art replacement approaches, menisci have been replaced with prostheses composed of permanent artificial materials. Such prosthesis have been constructed of purely artificial materials in order to minimize the possibility of an immunological response. In addition, the use of such materials is believed to be advantageous because it permits construction of a structure which can withstand the high and repeated loads which are encountered in the knee joint, and because it can alter the joint mechanics in beneficial ways that biological materials would not tolerate.

For example, a Teflon net has been used to replace the resected meniscus of a dog upon which fibrous ingrowth or regeneration was observed, although accompanied by significant chondral abrasion. A prosthetic meniscus has also been constructed from resilient materials such as silicone rubber or Teflon with reinforcing materials of stainless steel or nylon strands (U.S. Patent No. 4,502,161) A meniscal component has also been made from resilient plastic materials (U.S. Patent No. 4,085,466). In addition, reconstruction of meniscal lesions has been attempted with carbon-fiber-polyurethane-poly (L-lactide), but its success with these materials is minimal (Leeslag et al., Biological and Biomechanical Performance of Biomaterials - (Christel et al., eds.) Elsevier Science Publishers B.V., Amsterdam. 1986, pp: 347-352).

A prosthetic meniscus according to the features of the preamble of claim 1 is known from WO-A-8900413.

However, the replacement of meniscal tissue with structures consisting of permanent artificial materials generally has been unsuccessful, principally because the opposing articular cartilage of human and animal joints is fragile. The articular cartilage in the knee will not withstand abrasive interfaces, nor compliance variances from normal, which eventually results from the implantation of prior art artificial menisci. Additionally, joint forces are multiples of body weight which, in the case of the knee and hip, are typically encountered over a million cycles per year. Thus far, prior art permanent artificial menisci have not been composed of materials having natural meniscal properties, nor have they been able to be positioned securely enough to withstand such routine forces.

Therefore, what is needed is an improved prosthetic meniscus composed of biocompatible materials which are soft and lubricating.

Repair of other tissues such as skin and nerve has been attempted using both synthetic and natural materials. For example, Yannas et al., fashioned endodermal implants, and artificial epidermis out of natural collagen and glycosaminoglycans (U.S. Patent No. 4,060,081). Nylles et al. (Trans. Am. Soc. Artif. Intern. Organs (1983) 29:307-312) reported the use of synthetic resorbable polyesters for peripheral nerve regeneration applications, and the use of collagen conduits as a scaffold for nerve regeneration.

However, even with the foregoing technologies which have been applied to the reconstruction of anatomical structures other than knee joints, a structure suitable as a prosthetic meniscus and constructed from totally resorbable natural materials, or analogs thereof, has not been developed in the prior art.

Accordingly, it is an object of this invention to provide an improved meniscal prosthesis which allows for normal joint motion.

Another object is to provide a meniscal replacement or prosthesis which is biomechanically able to withstand normal joint forces and is able to function at those loads to protect the cartilage and stabilize the joint.

Yet another object is to provide a resorbable meniscal prosthesis which acts as a temporary in vivo scaffold for meniscal fibrocartilage infiltration and regeneration.

Still another object is to provide a meniscal prosthesis which is composed of biocompatible materials having an organization equivalent to that of the normal meniscus.

A further object is to provide a meniscal prosthesis which is adapted for implantation by standard operative techniques.

Still a further object is to provide a method by which such prosthetic menisci can be fabricated.

Summary of the Invention

The present invention provides a biocompatible and bioresorbable structure for implantation into the knee joint which assumes the form and role of a meniscus. This prosthetic meniscus promotes and provides a scaffold for the regeneration of tissue having the physical characteristics of a natural meniscus.

The prosthetic meniscus of the present invention is generally a dry, porous matrix of biocompatible bioresorbable fibers, including natural polymers or analogs or mixtures thereof. The matrix is adapted to have in vivo an outer surface contour substantially the same as that of a natural meniscus. Further, the matrix has pore size in the range of greater than 50 microns to less than about 500 microns. With this configuration, the matrix establishes an at least partially bioresorbable scaffold adapted for ingrowth of meniscal fibrochondrocytes. The matrix may have the shape of a circumferentially extending wedge spanning a predetermined angle greater than 0 degrees, and less than or equal to 360 degrees, and having a thickness in its central region which is less than its thickness in its peripheral regions. In some forms of the invention, the matrix may assume the shape of a simple wedge, a crescent-shaped wedge with a wide central region between two narrow distal tip regions, or a circumferentially extending wedge spanning an angle of 360 degrees and having a depressed (concave) central region, for example.

The matrix is composed of biocompatible and bioresorbable fibers, a portion of which may be crosslinked. The fibers include a natural material or an analog of a natural material such as a biosynthetic analog. In a preferred embodiment of the invention, the fibers of the matrix are polymers of, for example, natural molecules such as those obtained from animal or human tissue. Natural fibers useful for the same purpose include collagen, elastin, reticulin, analogs thereof, and mixtures thereof.

In some forms of the invention, the fibers may be randomly orientated throughout the matrix, or may be ordered at specified regions. Alternatively, the fibers may assume substantially circumferentially extending or substantially radially extending orientations throughout the prosthetic meniscus.

The matrix may also include glycosaminoglycan molecules (GAGs) interspersed with the fibers. GAGs are any mucopolysaccharide molecules which provide lubrication and crosslinks for the prosthetic meniscus of the invention. In the preferred aspects of the invention, GAGs such as chondroitin 4-sulfate, chondroitin 6-sulfate, keratan sulfate, dermatan sulfate, heparin sulfate, hyaluronic acid, and mixtures thereof are a component of the matrix. These GAGs may be uniformly dispersed throughout the prosthetic meniscus as individual molecules, or may be present in varying amounts in different regions of the structure.

In various forms of the invention, GAGs may directly participate in covalent crosslinking formation with the fibers, or may interact with the fibers mechanically in the form of entanglement or through interlocking mechanisms, forming stable fiber-GAG complexes.

The matrix include about 75-100% natural and/or synthetic fibers and about 0-25% GAGs by dry weight, the proportions of which may be constant throughout the structure or may be variable.

In a preferred embodiment of the invention, the matrix has a density of about 0.07 to 0.50 g matrix/cm^3 where "g matrix/cm^3" is a unit connoting the number of grams in a cubic centimeter of the matrix. In addition, it has an interfibrillary and interfibrillary space of about 2 to 25 cm^3/g matrix.

In another form of the invention, the prosthetic meniscus may further comprise a mesh composed of a bioresorbable, biocompatible material which is attached to portions of the outer surface of the matrix. The mesh aids in the successful implantation of the prosthetic meniscus into the knee joint by providing a temporary anchoring mechanism.

Further, the invention includes a method for fabricating a prosthetic meniscus of the type described above. Generally, the method includes placing a plurality of fibers and/or fibers and GAGs into a mold having a shape useful for knee joint function, subjecting the fibers (and GAGs) in the mold to two cycles of freezing and thawing, contacting said fibers or said fibers and GAGs with a chemical crosslinking reagent such that the fibers then assume the shape of the mold, and lyophilizing the resulting structure to obtain a dry, porous, volume matrix.

The fibers may be laid down in a circumferential orientation by rotating the mold as they are placed therein. Alternatively the fibers in the mold may be compressed with a rotating piston. Radial orientation of the fibers is produced by manually painting the fibers in a linear, radially directed fashion.

Specific densities and pore sizes may be obtained in various regions of the matrix by compressing the fibers or fibers and GAGs in the mold prior to the second freeze-thaw cycle, subsequent to the chemical crosslinking step. This may be accomplished by applying pressure to a specific region of the matrix with a piston of a predetermined shape.

In a preferred aspect of the invention, the cross linking step is performed using chemical agents which form intramolecular and intermolecular crosslinks. Useful chemical agents include, for example, glutaraldehyde, formaldehyde, biocompatible bifunctional aldehydes, carbodiimides, hexamethylene diisocyanate, bis-ionidates, glyoxal, polyglycerol polyglycidyl ether, glyoxal, and mixtures thereof. Particularly useful crosslinking agents are 1-ethyl, 3-(3-dimethylaminopropyl), polyglycerol polyglycidyl ether, and glutaraldehyde.

In other aspects of the invention, an additional crosslinking step is performed by lyophilizing the chemically crosslinked matrix and then subjecting it to dehydrothermal crosslinking procedures.

The invention will next be described in connection with certain illustrated embodiments. However, it should be clear that various modifications, additions, and deletions can be made without departing from the spirit or scope of the invention.

Brief Description of the Drawings

The foregoing and other objects of this invention, the various features thereof, as well as the invention, itself, may be more fully understood from the following description, when read together with the accompanying drawings.

FIG. 1 shows a simplified diagramatic representation of a human knee joint, with menisci in native positioning;

FIG. 1A is a diagrammatic representation of a cut-away view of the knee joint showing the medial and lateral menisci as they are positioned in vivo over the medial and lateral condyles.

FIG. 2 shows a perspective view of an exemplary prosthetic meniscus in accordance with the present invention;

FIG. 3 shows a perspective radial section of the prosthetic meniscus of FIG. 2;

FIG. 4 shows a perspective view of an alternative embodiment of the present invention;

FIG. 5 shows a sectional view along line 5-5 of the prosthetic meniscus of FIG. 4.

FIG. 6 shows a mold designed for the fabrication of a prosthetic meniscus having a cylindrical pad shape.

FIG. 7 shows a mold designed for the fabrication of a prosthetic meniscus having a crescent-shaped wedge form.

FIG. 8 shows a mold designed for the fabrication of a cylindrical prosthetic meniscus.

FIG. 9 is a photographic representation of in vivo meniscal regrowth after 80% resection and implantation of the prosthetic meniscus.

FIG. 10 is a photographic representation of an explanted canine meniscus containing a section of scaffold, and demonstrating in vitro regrowth of meniscal tissues into the scaffold.

FIG. 11 is a photographic representation of two canine knee joints three months after surgical resection.

FIG. 12 is a series of graphs showing the hydrodynamic profiles of the proteoglycan aggregates in the regenerated meniscus (FIG. 12B) compared to the resected rim alone (FIG. 12D), and compared with control samples including the remaining fibrocartilage post-resection in the medium (FIG. 12A) and the remaining fibrocartilage post-resection in the associative extract (FIG. 12C).

Description of the Invention

It has been discovered that a prosthetic meniscus fabricated from biocompatible and bioresorbable fibers can be surgically implanted into the knee joint so as to provide normal joint motion and strength. This

prosthetic meniscus also acts as a scaffold for regenerating meniscal tissue whose ingrowth is encouraged by the physical characteristics of the implanted device.

FIG. 1 shows a diagramatic representation of the normal positioning of medial meniscus 7 and lateral meniscus 8 in the human knee joint 3 between the femur 2 and tibia 4. These menisci, when compressed between the femur 2 and tibia 4, become tough except at their points of attachment. FIG. 1A shows the in vivo structure of medial meniscus 7 and lateral meniscus 8 in the knee joint 3. The menisci conform to the shapes of the surfaces between which they are positioned, thereby resulting in two distinct in vivo forms. For example, the medial meniscus 7 has a relatively open crescent shape, while the lateral meniscus 8 has a relatively closed crescent shape.

An exemplary prosthetic meniscus 10 is shown in FIG. 2. The prosthetic meniscus 10 is a generally wedge-shaped, porous dry matrix or scaffold which extends circumferentially or laterally at least in part about a central axis 11. In the preferred form, the prosthetic meniscus 10 has the shape of a crescent-shaped wedge, extending circumferentially about the axis 11, and comprising a relatively wide central region 12 between two narrow distal regions 14 and 16. In the preferred form, the wedge has maximum height A at its peripheral edge of approximately 1 cm (0.4 inches) a height D at its central point of approximately 0,5 cm (0.2 inches), and a maximum radial dimension C of approximately 2,5 cm (1.0 inches). The crescent shaped wedge subtends an angle B about axis 11 substantially in the range of about 135 to about 155 degrees, and preferably of about 150 degrees.

In the embodiment illustrated in Fig. 2, the prosthetic meniscus 10 includes a mesh member 20 extending from its peripheral edge. The mesh member 20 is composed of a biocompatible, bioresorbable material, and provides a readily used means for anchoring the array 10 in place. The mesh member 20 may function in this capacity until sufficient tissue ingrowth occurs to then provide that function. By way of an example, the mesh member 20 may be a #1 mesh screen composed of absorbable suture materials such as polyglyconate, Dexon, or polydioxane (PDS) woven into a mesh. Non-absorbable suture materials such as Goretex® may also be used.

FIGs. 4 and 5 show an additional embodiment of the present invention which is similar in composition to the prosthetic meniscus depicted in FIG. 2. More particularly, FIG. 4 depicts a right circular cylinder-shaped meniscus 22, extending fully about axis 11, i.e. where angle B equals 0 degrees. (i.e. the meniscus subtends 360 degrees.) FIG. 5 shows a sectional view along line 5-5 of the meniscus shown in FIG. 4. The device illustrated in Figs. 4 and 5 show the shape of the meniscus 22 when implanted; that is, the height D at areas 11 is less than the peripheral height A of the device. Prior to implantation, the device 22 may in some cases not have this relationship but upon implantation, the normal loads applied by the body force this conformation.

In alternative forms of the invention, still other shapes may be used. For example, it is not required that the wedge be symmetrical. These embodiments may have densities of collagen fibers and dispersions of GAG molecules and crosslinks, permitting accommodation of differing stress levels, rates of ingrowth, and resiliency. Differing densities may be obtained in vivo where a device having uniform density is implanted, and body loading causes non-uniform compression of the device.

The prosthetic meniscus may be fabricated of any biocompatible, bioresorbable fibers which include a natural material or an analog thereof; preferably polymeric in structure, which can provide mechanical strength and protection and lubrication while encouraging tissue ingrowth (e.g., collagen, reticulin, elastin, cellulose, or biosynthetic analogs thereof). These fibers may be ordered in substantially circumferentially-extending or substantially radially-extending orientations, with the density of fibers being substantially uniform throughout the matrix. Alternatively, the matrix fibers may be unordered. In either the ordered or unordered configuration, the density of the fibers may be non-uniform. In the non-uniform configuration, relatively high densities of fibers may be established at anticipated points of high stress by local application.

In an alternative aspect of the invention, the intrafibrillary and interfibrillary space is relatively high, a condition which promotes ingrowth of regenerated meniscal tissue. For example, the density of the meniscus may be in the range of about 10-25 g matrix/cm^3. Alternatively, the intrafibrillary and interfibrillary space is relatively low, a condition which provides cushioning, lubrication, and mechanical support for the knee joint and which retards tissue and cell ingrowth, thereby diminishing the rate of scaffold resorption (e.g., density is in the range of about 2-10 g matrix/cm^3).

The temporary stability of the shape of the structure when in vivo, and the rate of meniscal resorption, are both attributed to the effective crosslinking formation between at least one portion of the fibers. The crosslinking reagents used may be any biocompatible bifunctional reagents which interacts with amino groups, carboxyl, or hydroxyl groups on a single fiber (intramolecular crosslinks), or the fibers or on the fibers and the GAGs, resulting in covalent bond formation between adjacent molecules (intermolecular crosslinks). Useful crosslinking reagents include aldehydes, hexamethylene diisocyanate, bis-imidates,

polyglycerol polyglycidyl ether, and carbodiimides.

The crosslinked device maintains sufficient degree of hydrophilicity and elasticity which simulates the properties of the natural meniscus, i.e., ability to sustain mechanical stress and to protect and lubricate articular surfaces. In addition, the structure provides an ideal environment for cell infiltration and extracellular matrix synthesis and deposition resulting in regeneration of natural meniscal tissue.

GAGs may be dispersed throughout the fibers. Alternatively, they may act as intermolecular crosslinks between fibers. These GAG crosslinks are composed typically of at least one of the group of molecules consisting of chondroitin 4-sulfate, chondroitin 6-sulfate, keratin sulfate, dermatan sulfate, heparin sulfate, and hyaluronic acid. The dispersion of GAG crosslinks is preferably uniform, but may be more concentrated at anticipated points of high stress, typically at the distal regions 14 and 16, and less concentrated in the central region 12 (FIG. 1). In such configurations, the GAG concentration may be in the range of about 0-25% in the distal regions 14 and 16, and in the range of about 0-10% in the central region 12. However, when uniform, the dispersion of GAG throughout the prosthetic meniscus may be, for example, in the range of about 1-15%.

Intermolecular cross linkages can also be established through a dehydrothermal process (heat and vacuum) which results in peptide bond formation between an epsilon amino group of lysine or hydroxylysine and a carboxyl group of aspartic or glutamic acid.

The cross linked device has a relatively high thermal stability between about 55-85° C, preferably between about 65-75° C, for sufficient in vivo stability. This may be achieved through manipulation of the crosslinking conditions, including reagent concentration, temperature, pH, and time.

In a one embodiment the prosthetic meniscus is constructed mainly of Type I collagen fibers without GAG crosslinks. Type I collagen fibers may be obtained from the Achilles tendons of animals. However, the fibers may also be obtained from animal skin or from the skin or tendon of humans. The tissues are treated with a series of mechanical and chemical means to either totally remove the non-collagenous materials or reduce them to a minimal level. In the preferred processing steps, the tendon or skin is mechanically disintegrated into fine pieces useful for further processing. The disintegration may be achieved by grinding the tissue at liquid nitrogen temperature, or by cutting the tissue into small pieces with a sharp knife. In certain applications, the tendons are mechanically disintegrated along the fiber direction in order to maintain the length of the fibers for mechanical strength.

Salt extraction of tendon at neutral pH removes a small portion of the collagen molecules that are newly synthesized and have not yet been incorporated into the stable fibrils. Salt also removes some glycoproteins and proteoglycans that are associated with collagen through electrostatic interactions. Other salts such as KCl and the like can be used as a substitute for NaCl.

Lipids that are associated with the cell membranes or collagenous matrices may be removed by first extracting with detergents such as Triton X-100, followed by extracting with ether-ethanol mixtures. The concentration of Triton X-100 is usually about 2-4%, but is preferably about 3%. The preferred mixture of ether-ethanol is usually at about a 1:1 ratio (v/v). The period of extraction is usually from 8 hours to 96 hours, as is preferably from about 24 to 48 hours.

Further extraction may be accomplished by matrix swelling conducted at two extreme pHs. Both acidic and basic swelling weakens the non-covalent intermolecular interactions, thus facilitating the release of non-covalently attached glycoproteins, glycosaminoglycans (GAGs), and other non-collagenous molecules through the open pores of the collagenous matrices.

The swelling of matrix at alkaline pH is done by treating the collagen at high pH with $Ca(OH)_2$, NaOH, or the like, for a period of about 8-96 hours. Alkali extraction in the presence of triple-helical stabilizing salts such at $(CH_3)NCl$, NH_3S0_4, or the like reduces the potential risk of denaturation of the collagen. Alkali treatment dissociates the non-cross-linked glycoproteins and GAGs from the collagen matrices. The alkali also removed the residual lipids through saponification.

The acid swelling may be conducted at a low pH in the presence of acetic acid, HCl, or the like. Like the alkali treatment, the acid swelling removes non-cross-linked glycoproteins and GAGs.

The non-triple helical portions of the molecule (telopeptides) are involved in intermolecular crosslinking formation. They are weak antigens and are susceptible to attack by proteases, such as pepsin, trypsin, and the like. Prolonged digestion with such proteases dissociates the fibrils (fibers) into individual molecules. However, if the digestion process is properly controlled such that maximal telopeptides are removed without complete dissociation, the immunogenic properties of the fibrils can be reduced to a minimal level without compromising the mechanical strength. For example, to isolate molecular collagen, the digestion of skin or tendon with pepsin is usually conducted at an enzyme:collagen ratio of about 1:10 for about 24-96 hours at below room temperature. In comparison, fibrils may be obtained by limited pepsin digestion achieved at a ratio of about 1:100 (enzyme:collagen) for about 24-96 hours at 4° C.

Collagen fibers obtained according to this methodology are then used to fabricate the prosthetic meniscus of the present invention. However, it must be appreciated that collagen obtained from other sources, such as biosynthetically-produced collagen or analogs thereof - may also be used in the construction of the prosthetic meniscus.

In one embodiment, the prosthetic meniscus further includes an adhesion molecule or adhesive portion or analog thereof which is incorporated within the network of fibers, and which alds in meniscal tissue regeneration Useful adhesion molecules include peptides such as fibronectin (see e.g., U.S. Patent No. 4,589,881, 4,661,111 and 4,578,079), a portion of which can be conjugated to, for example, chondroitin sulfate.

The method of fabrication includes molding the collagen fibers into a predetermined shape using, for example, the mold forms described below in conjunction with FIGs. 6-8. The fibers may be placed randomly in the mold, or may be oriented in specific directions to achieve a meniscus having specific structure characteristics. Other components such as GAGs which may participate in the crosslinking reaction, can be mixed in with the fibers in a random or non-random fashion before the structure is subjected to various crosslinking and dehydrating procedures including various chemical and/or dehydrothermal methods. Adhesion molecules or adhesive fragments or analogs thereof may be added to the structure before the final drying step by soaking the structure in a solution containing that molecule, or by specifically coupling it to an existing fiber or crosslink. For example, the adhesion portion of fibronectin may be cross linked to chondroitin sulfate at a concentration of 3 peptide molecules per molecule chondroitin sulfate by soaking the prosthetic meniscus in a 50 mg/ml solution thereof.

By following the processes described in the above examples set forth herein below, a prosthetic meniscus of the form shown in FIGs. 2 or 3 may be constructed having the characteristics listed below in TABLE 1.

TABLE 1

Physical Characteristics

height A = 0,5-1cm (0.20 - 0.40 inches)
angle B = 25 - 45 degrees
radius C = 1,3-5cm (0.5 - 2.0 inches)
height D = 0,13-0,25cm (0.05 - 0.10 inches)
Density = 0.07 - 0.5 g/cm^3
Intra- and Interfibrillary space = 2-25 cm^3/g matrix

Constituents

fiber (collagen) content = 75-100%
GAG content = 0-25%

The following non-limiting examples describe methods of fabrication and in vivo testing of the prosthetic meniscus of the invention.

EXAMPLE 1

Mold Fabrication:

A mold 100 useful for fabricating the prosthetic meniscus is made of implantable stainless steel or biocompatible plastics such as teflon, polypropylene, delrin, or combination of these materials. The mold 100 is composed of three pieces 102, 104, and 106 as shown in FIGs. 6-8.

By way of example for the disk-shaped meniscus illustrated in FIGs. 4 and 5, the mold 100 of FIG. 6 is used. The first piece 102 is disk-like and has a diameter substantially equal to that of the desired meniscus. Piece 102 is perforated to allow liquid to pass through under pressure. The inner surface 103 of piece 102 has the desired shape of one side of the meniscus-to-be-formed.

The second piece 104 is a hollow cylinder which has the same inner dimension as the first piece 102. The third piece 106 is a cylindrical piston which has an outer diameter slightly less than the inner diameter of piece 104. The "top", or crown, surface 108 of piston 106 has the desired shape of one side of the meniscus-to-be-formed.

For the meniscus of FIG. 3, the mold of FIG. 7 is used where the shape of piece 102, and cross-section of piece 104 have the shape of an angular segment. For a flat circular disk meniscus, the mold 100 of FIG. 8 is used where pieces 102 and 104 are the same as in FIG. 6 and piece 106 is similar to that piece in FIG. 108 but has a flat crown surface 108.

During fabrication of the meniscus 10, the piece 102 is first assembled within piece 104, as shown in FIGs. 6-8. The constituent fibers (in a fluid) are placed against the surface 103 of piece 102. Then the crown surface 108 of piston 106 is driven toward surface 103 along a compression axis 106a until the fibers are compressed, the fluid is driven out through piece 102, and the desired axial dimension of the compressed fiber array is attained. The mold is then frozen in preparation for chemical crosslinking.

EXAMPLE 2

Preparation of Purified Type I Collagen

A) Tissue:

Bovine, porcine, or sheep Achilles tendon is obtained from USDA-approved slaughter houses. The preferred age of the animals is between 12-18 months. The tissue is kept cold during the purification process except where specified to minimize bacteria contamination and tissue degradation.

B) Mechanical Disintegration:

The adhering tissues of carefully selected tendons are first scrapped off mechanically. The tendons are then minced or cut into fine pieces and washed in excess quantities (10 volumes) of cold water to remove residual blood proteins and water soluble materials.

C) Salt Extraction:

The washed tendons are extracted in ten volumes of 5% NaCl, 0.01 M Tris, pH 7.4, for 24 (+/-4) hours to remove salt soluble materials. The salt extracted tendons are repeatedly washed in about 10 volumes of water to remove the salt.

D) Lipid Extraction:

The material is extracted in 3% Triton X-100 for 24 (+/- 2) hours. The detergent is removed by extensive washing with water. The material is then extracted in 3-4 volumes of ether-ethanol (1:1 vol/vol) for 24 (+/- 2) hours to further minimize the lipid content. The lipid extracted material is extensively washed in water to remove the ether and ethanol.

E) Matrix Swelling:

The material is then subjected to two extreme pH extractions to remove non-collagenous materials. Alkaline extraction is conducted with 3-4 volumes of 0.2 M NaOH at pH 12.5 - 13.5 at room temperature (RT) in the presence of 1.0 M (CH)NCl for 24 (+/- 2) hours with mild agitation.

Following alkaline extraction, the pH is neutralized with HCl and the material is washed with water. The pH is then adjusted to 2.5 - 3.0 by adding concentrated acetic acid to a final concentration of 0.5 M. The acid extraction is continued for 24 (+/- 2) hours with agitation.

F) Limited Proteolytic Digestion:

The acid swollen tendon is then subjected to a limited proteolytic digestion with pepsin (enzyme : collagen = 1 : 100) for 24 (+/-) 2 hours. The pepsin and telopeptides are removed through dialysis.

The swollen fibrillar material is then coacervated by adjusting the pH to its isoionic point with 1 M NaOH or HCl or by adjusting the ionic strength to 0.7 with NaCl. The aggregated collagen fibers are harvested by filtration, and the filtered material extensively washed with cold buffered solution. The highly purified type I collagen may be stored (-20 to -40 • C) until used.

EXAMPLE 3

Device I Fabrication

A) The collagen content of the highly purified type I collagen fibrils from EXAMPLE 2 is determined either by gravimetric methods or by determining the hydroxyproline content assuming a 13.5% by weight of hydroxyproline in type I collagen. The amount of purified material needed to fabricate a given density of a meniscus device is then determined and weighed.

B) A solution of fibrillar collagen is carefully fit into a mold of specified dimensions, e.g. according to the exemplary meniscus described above in conjunction with FIG. 2-5 (see EXAMPLE I and FIGs. 6-8 for the description of molds). Collagen fibers are laid down in random manner or in an oriented manner. In the oriented manner, circumferential orientation of the fibers is produced by rotation of the piston about its principal axis as the material is compressed in the mold; radial orientation is produced by manual painting of the collagen fibers in a linear, radially directed fashion.

C) The fibers are frozen at -20 • C, turned out of the mold, and thawed at RT.

D) The fibers are then resuspended in phosphate buffered saline, put back into the mold in the desired orientation(s), and compressed with the piston.

E) The compressed fibers are then refrozen at -20 C and then thawed at RT.

F) The resulting structure is cross linked by soaking in a 0.2% glutaraldehyde solution, pH 7.6, for 24 (+/- 0.5) hours. Each glutaraldehyde-cross-linked meniscal device is subsequently rinsed repeatedly in 500 ml of phosphate buffered saline (PBS) solution, pH 7.4, for 4, 8, 24 and 48 hours.

G) The rinsed matrix is then lyophilized.

EXAMPLE 4

Device II Fabrication

A)-G) (same as in EXAMPLE 3)

H) The lyophilized matrix is subjected to dehydrothermal crosslinking by vacuum and heat. The vacuum is first applied to reduce the residual water content to a minimal level (some structural water, about 3%, may still be associated with collagen triple-helix as part of the structure stabilizing factor). The heat is increasing in steps to 110 • C (+/- 5 •), and continually applied at 110 • C under vacuum for 24 (+/- 2) hours.

EXAMPLE 5

Device III Fabrication

A) (same as in EXAMPLE 3)

B) The collagen material is dispersed in 0.01 M HCl solution at pH 2-2.5. Predetermined amounts of various GAGs are weighed and dissolved in water. For example, for a given density of 0.25 g/cm, the collagen content will be 0.244 g, the hyaluronic acid content will be 0.003 g, and the chondroitin sulfate content will be 0.003 g for a 2.5% GAG content. The GAG solution is mixed in with the collagen solution and placed in the mold in the desired orientation as described in EXAMPLE 2.

C)-G) (same as in EXAMPLE 3)

EXAMPLE 6

Device IV Fabrication

A)-C) (same as in EXAMPLE 3)
D) (same as in EXAMPLE 3 except that the fibers laid down are not compressed.
E)-G) (same as in EXAMPLE 3)

EXAMPLE 7

Device V Fabrication

A)-E) (same as in EXAMPLE 3)
F) The molded collagen is cross linked in 5% polyglycerol polyglycidyl ether in 50% ethanol and 0.1 M Na_2CO_3 at pH 10.0 for 24 (+/- 2) hours. The crosslinked device is rinsed for 4, 8, 24 and 48 hours, each with 500 ml of PBS, pH 7.4.
G) (same as in EXAMPLE 3)

EXAMPLE 8

Device VI Fabrication

A)-E) (same as in EXAMPLE 3)
F) The molded collagen is crosslinked in the presence of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (10 mg/g matrix) in 0.9% NaCl, pH 4.7 at room temperature for 24 (+/- 2) hours. The addition of carbodiimide is made every 3-4 hours, and the pH is adjusted to 4.7 after each addition of carbodiimide.
G) (same as in EXAMPLE 3)

EXAMPLE 9

Device VII Fabrication

(A) - (D) same as steps (A) - (D) as described in Example II.
(E) For attachment purposes, a mesh of absorbable polyglyconate suture material, matched to the size of the mold, is laid in the dispersed collagen such that it protrudes from the structure's periphery to form a skirt which may extend over the tibial plateau. This mesh provides both immediate attachment sites and long term fibrous ingrowth.

EXAMPLE 10

Testing

The prosthetic menisci were evaluated in vivo using animal models and in vitro to determine ability to function or to serve as a regeneration template for normal meniscal tissues.

1. In vivo Studies

Seventeen prosthetic menisci (device III type) were implanted into eleven immature Yorkshire pigs. Seven joints underwent a two-thirds subtotal resection of the medial meniscus with replacement by a matched prosthetic meniscus; two joints underwent a two-thirds subtotal resection alone; two joints received a similar subtotal meniscectomy with the resected portion immediately replaced with suture fixation; and two joints received total meniscectomy alone.

Evaluation of all joints was made at 3 or 6 weeks. All arthrotomies healed well, and all animals progressed to full weight bearing. At final evaluation all prosthetic material had been partially or completely resorbed without evidence of joint destruction or cartilage abrasion. Neovascularization was observed as the basic healing mechanism in both the prosthetic implanted menisci as well as in the controls, and in all joints there was evidence of early meniscal regeneration. The prosthetic meniscus material conformed to the appropriate joint shape. In addition, there was no clinical evidence of implant rejection over a 6 week period.

Histologically, there was acute inflammation followed by neovascularization and extensive fibroplasia with early hyalinization of the newly formed collagen. (See FIG. 9)

In vivo studies of the invention in mature dogs have demonstrated induced meniscal regeneration through the prosthetic material. Normally, the mature canine stifle is known to not regenerate a meniscus and is known to develop significant arthritic changes. However, six weeks after meniscectomy and implantation of scaffolds in accordance with the present invention, there occurred significant regeneration of the meniscus through the scaffolds. The scaffolds provided joint protection, as determined by diminished cartilage erosions, osteophyte formation and affinity for India ink.

FIG. 11 is a photographic representation of two canine knee joints three months after surgical resection. The joints were protected by the prosthetic implant with subsequent regrowth of a new meniscus. The joint on the right in FIG. 11 underwent an 80% meniscal resection alone. The dramatic articular cartilage protection is highlighted by India ink.

New collagen and glycosaminoglycan formation was evidenced histologically, by Alcian Blue and Masson's Trichrome stains.

The hydrodynamic size and chromatographic profiles of the proteoglycans synthesized within both the meniscal implants and the controls were similar when analyzed on a Sephacryl S-500 column as shown in FIG. 12. FIG. 12 is a series of graphs showing the hydrodynamic profiles of the proteoglycan aggregates in the regenerated meniscus (FIG. 12B) compared to the resected rim alone (FIG. 12D), and compared with control samples including the remaining fibrocartilage post-resection in the medium (FIG. 12A) and the remaining fibrocartilage post-resection in the associative extract (FIG. 12C).

2. in vitro Studies

Menisci were aseptically harvested from mature dogs, trimmed of all adherent tissue, and placed into Gey's balanced saline solution. Each meniscus was bisected in the coronal plane and 3 mm full-thickness circular defects were made in each meniscal half. The defects were filled with a 3 mm diameter plug of one of two prototypes of a complex collagen-based biosynthetic scaffold (prosthetic meniscus). The menisci were placed in six well culture plates containing six ml of Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum, sodium ascorbate, and 0.1% penicillin/streptomycin. Cultures were maintained at 37 • C in a humidified atmosphere of 10% CO_2/90% air, fed three times per week, and placed in fresh culture wells every week to prevent the formation of explant cell cultures. At intervals of one, four, and six weeks after initiation of culture, three menisci from each group were removed, fixed, and evaluated with serial sections and staining.

The results (shown in FIG. 10) demonstrated increasing cellular migration and invasion over time. There was no apparent toxicity from the material. The morphologic characteristics of the migrating cells were more fusiform and elongated than native fibrochondrocytes The depth of cellular penetration into the scaffold appeared to be limited by the density of the prosthetic complex.

The present invention may be embodied in other specific forms without departing from the essential characteristics thereof. The present embodiments are therefore to be considered in all respects as illustrative and not restrictive, the scope of the invention being indicated by the appended claims rather than by the foregoing description, and all changes which come within the meaning of the claims are therefore intended to be embraced therein.

Claims

1. A prosthetic meniscus comprising a dry porous matrix of biocompatible and at least partially bioresorbable fibers,
said fibers including natural polymers, e.g. collagen, elastin, reticulin, cellulose, or analogs or mixtures thereof,
said matrix being adapted to have in vivo an outer surface contour substantially the same as that of a natural meniscus, characterised in that
said matrix has pore size in the range of greater than 50 microns to less than about 500 microns,
whereby said matrix establishes an at least partially bioresorbable scaffold adapted for ingrowth of meniscal fibrochondrocytes.

2. A prosthetic meniscus according to claim 1 wherein said matrix has a substantially wedge shape including a wide central region between two narrow distal tip regions.

3. A prosthetic meniscus according to claim 1 wherein said matrix has a density of about 0.07 to 0.50 gram matrix per cubic centimeter.

4. A prosthetic meniscus according to claim 1 wherein said matrix has an interfibrillary and interfibrillary space of about 2 - 25 cubic centimeters per gram matrix.

5. A prosthetic meniscus according to claim 1, wherein said natural polymers comprise Type I collagen, and wherein said collagen fibers are present at a concentration of about 75-100% by dry weight, and said glycosaminoglycan molecules are present at a concentration of about 0-25% by dry weight.

6. A prosthetic meniscus according to claim 1 further comprising a plurality of glycosaminoglycan molecules, e.g. chondroitin 4-sulfate, chondroitin 6-sulfate, keratan sulfate, dermatan sulfate, heparin sulfate, hyaluronic acid, and mixtures thereof, interspersed with said fibers, at least a portion of said molecules providing crosslinks between ones of said fibers.

7. A prosthetic meniscus according to claim 6 wherein said fibers are present at a concentration of about 75-100% by dry weight, and said glycosaminoglycan molecules are present at a concentration of about 0-25% by dry weight.

8. A prosthetic meniscus according to claim 1 wherein said matrix has the shape of a circumferentially extending wedge, e.g. a crescent-shaped wedge, having a central region and a region peripheral thereto, and spanning a predetermined angle greater than 0 degrees and less than or equal to 360 degrees about said central region, and

where the thickness in said central region of said wedge is less than the thickness in the peripheral region of said wedge.

9. A prosthetic meniscus according to claim 1 further comprising a mesh extending from portions of the outer surface of said matrix, said mesh being resorbable and biocompatible.

10. The prosthetic meniscus according to any one of claims 1 to 9 for use in therapy, e.g. in a method of regenerating meniscal tissue in vivo comprising the steps of:
(a) fabricating the prosthetic meniscus according to any one of claims 1-9; and
(b) implanting said prosthetic meniscus into a knee joint by surgical procedures.

11. The prosthetic meniscus of claim 10 wherein said prosthetic meniscus fabricated in step (a) assumes the shape of a native meniscus when implanted in step (b).

12. A method for fabricating a prosthetic meniscus according to any one of claims 1-9, comprising the steps of:
(a) placing a plurality of biocompatible and bioresorbable fibers into a mold, said fibers including natural polymers, e.g. collagen, elastin, reticulin, cellulose, or analogs or mixtures thereof, and said mold defining a shape for a meniscal prosthesis that enables knee joint function;
(b) subjecting said fibers to a first and a second cycle of freezing and thawing;
(c) contacting said fibers with a chemical crosslinking agent, e.g. glutaraldehyde, formaldehyde, biocompatible and bifunctional aldehydes, carbodiimides, hexamethylene diisocyanate, bis-imidates, polyglycerol polyglycidylether, glyoxal, and mixtures thereof, such that said fibers assume the shape of said mold; and
(d) lyophilizing said crosslinked fibers.

13. The method of claim 12 wherein said placing step further comprises placing a plurality of glycosaminoglycan molecules into said mold.

14. The method of claim 12 wherein said placing step further comprises the step of orienting said fibers substantially circumferentially.

15. The method of claim 14 wherein said orienting step comprises compressing said fibers in said mold with a piston, wherein piston motion is substantially directed along a compression axis, while during said compressing step said piston is rotated with respect to said mold about said compression axis.

16. The method of claim 14 wherein said orienting step comprises rotating said mold as said fibers are placed therein.

17. The method of claim 12 wherein said placing step further comprises the step of orienting said fibers substantially radially.

18. The method of claim 12 further comprising the step of compressing said fibers prior to said second cycle of freezing and thawing.

19. The method of claim 18 wherein said compressing step comprises applying a predetermined amount of pressure to a region of said matrix with a piston, said piston having a predetermined shape.

20. The method of claim 18 further comprising the additional step of subjecting said lyophilized matrix to a dehydrothermal crosslinking procedure.

21. The method of claim 12 wherein said placing step further comprises interspersing a plurality of glycosaminoglycan molecules such as chondroitin 4-sulfate, chondroitin 6-sulfate, keratin sulfate, dermatan sulfate, heparin sulfate, hyaluronic acid, and mixtures thereof.

Patentansprüche

1. Eine Meniskus-Prothese, die eine trockene, poröse Matrix biokompatibler und wenigstens teilweise bioresorbierbarer Fasern aufweist,
wobei besagte Fasern natürliche Polymere, z. B. Kollagen, Elastin, Retikulin, Cellulose oder Analoga oder Gemische davon umfassen,
wobei besagte Matrix, die adaptiert ist, in vivo eine im wesentlichen einem natürlichen Meniskus gleichende Außenflächenkontur zu besitzen, dadurch gekennzeichnet ist, daß
besagte Matrix eine Porengröße im Bereich von größer als 50 µm bis weniger als etwa 500 µm besitzt, wodurch besagte Matrix ein wenigstens teilweise bioresorbierbares Gerüst bildet, das für das Einwachsen von Meniskusfibrochondrocyten adaptiert ist.

2. Eine Meniskus-Prothese nach Anspruch 1, worin besagte Matrix im wesentlichen eine Keilform besitzt, einschließlich eines breiten Zentralbereichs zwischen zwei schmalen distalen Endbereichen.

3. Eine Meniskus-Prothese nach Anspruch 1, worin besagte Matrix eine Dichte von etwa 0,07 bis 0,50 Gramm Matrix pro Kubikzentimeter besitzt.

4. Eine Meniskus-Prothese nach Anspruch 1, worin besagte Matrix einen Intrafibrillär- und Interfibrillärraum von etwa 2-25 Kubikzentimeter pro Gramm Matrix besitzt.

5. Eine Meniskus-Prothese nach Anspruch 1, worin besagte natürliche Polymere Typ I Kollagen umfassen, und worin besagte Kollagenfasern in einer Trockengewicht-Konzentration von etwa 75-100% vorhanden sind, und besagte Glycosaminoglycan-Moleküle in einer Trockengewicht-Konzentration von etwa 0-25% vorhanden sind.

6. Eine Meniskus-Prothese nach Anspruch 1, die des weiteren eine Vielzahl an Glycosaminoglycan-Molekülen aufweist, z. B. Chondroitin-4-sulfat, Chondroitin-6-sulfat, Keratansulfat, Dermatansulfat, Heparinsulfat, Hyaluronsäure und Gemischen davon, die mit besagten Fasern durchsetzt sind, wobei wenigstens ein Teil besagter Moleküle Vernetzungen zwischen einzelnen besagten Fasern bereitstellen.

7. Eine Meniskus-Prothese nach Anspruch 6, worin besagte Fasern in einer Trockengewicht-Konzentration von etwa 75-100% vorhanden sind, und besagte Glycosaminoglycan-Moleküle in einer Trockengewicht-Konzentration von etwa 0-25% vorhanden sind.

8. Eine Meniskus-Prothese nach Anspruch 1, worin besagte Matrix die Form eines kreisförmig verbreiterten Keils, z. B. eines sichelförmigen Keils, besitzt mit einem Zentralbereich und außerdem einen Randbereich und sich über einen zuvor festgelegten Winkel von mehr als 0 Grad und weniger oder gleich 360 Grad um besagten Zentralbereich erstreckt, und wo die Dicke des besagten Zentralbereichs

des besagten Keils geringer als die Dicke des Randbereichs des besagten Keils ist.

9. Eine Meniskus-Prothese nach Anspruch 1, die des weiteren ein sich über Teile der Außenfläche besagter Matrix erstreckendes Geflecht umfaßt, wobei besagtes Geflecht resorbierbar und biokompatibel ist.

10. Eine Meniskus-Prothese nach einem der Ansprüche 1 bis 9 zur therapeutischen Verwendung, z. B. in einem folgende Schritte umfassenden Regenerationsverfahren von Meniskus-Gewebe in vivo:
(a) Herstellung der Meniskus-Prothese nach einem der Ansprüche 1 bis 9.
(b) chirurgische Implantierung besagter Meniskus-Prothese in ein Kniegelenk.

11. Die Meniskus-Prothese nach Anspruch 10, worin besagte, in Schritt (a) hergestellte Meniskus-Prothese die Form eines nativen Meniskus annimmt, wenn die Prothese in Schritt (b) implantiert wird.

12. Ein Herstellungsverfahren einer Meniskus-Prothese nach einem der Ansprüche 1 bis 9, das die Schritte umfaßt:
(a) Einlegen einer großen Anzahl biokompatibler und bioresorbierbarer Fasern in eine Form, wobei besagte Fasern natürliche Polymere einschließen, z. B. Kollagen, Elastin, Retikulin, Cellulose oder Analoga oder Gemische davon, und wobei besagte Form eine Form einer Meniskus-Prothese bestimmt, die eine Kniegelenkfunktion ermöglicht;
(b) Unterziehen besagter Fasern einem ersten und zweiten Zyklus von Gefrieren und Auftauen;
(c) In-Kontakt-Bringen besagter Fasern mit einem chemisch vernetzenden Agens, z. B. Glutaraldehyd, Formaldehyd, biokompatiblen und bifunktionellen Aldehyden, Carbodiimiden, Hexamethylen-Diisocyanat, bis-Imidaten, Polyglycerinpolyglycidylether, Glyoxal und Gemische davon, so daß besagte Fasern die Gestalt besagter Form annehmen; und
(d) Lyophylisieren besagter vernetzten Fasern.

13. Das Verfahren gemäß Anspruch 12, worin besagter Einlegeschritt des weiteren das Einbringen einer großen Anzahl an Glycosaminoglycan-Molekülen in besagte Form umfaßt.

14. Das Verfahren gemäß Anspruch 12, worin besagter Einlegeschritt des weiteren den Schritt der im wesentlichen kreisförmigen Ausrichtung besagter Fasern umfaßt.

15. Das Verfahren gemäß Anspruch 14, worin besagter Ausrichtungsschritt das Komprimieren besagter Fasern in besagter Form mit einem Kolben umfaßt, worin eine Kolbenbewegung im wesentlichen entlang einer Kompressionsachse gerichtet ist, wohingegen während besagtem Kompressionsschritt besagter Kolben bezüglich besagter Form um besagte Kompressionsachse gedreht wird.

16. Das Verfahren gemäß Anspruch 14, worin besagter Ausrichtungsschritt das Drehen besagter Form umfaßt, während besagte Fasern darin eingelegt sind.

17. Das Verfahren gemäß Anspruch 12, worin besagter Einlegeschritt des weiteren den Schritt der im wesentlichen radialen Ausrichtung besagter Fasern umfaßt.

18. Das Verfahren gemäß Anspruch 12, das des weiteren den Kompressionsschritt besagter Fasern vor besagtem zweiten Zyklus von Gefrieren und Auftauen umfaßt.

19. Das Verfahren gemäß Anspruch 18, worin besagter Kompressionsschritt das Ausüben eines zuvor festgelegten Drucks auf einen Bereich besagter Matrix mit einem Kolben umfaßt, wobei besagter Kolben eine zuvor festgelegte Form besitzt.

20. Das Verfahren gemäß Anspruch 18, das des weiteren einen zusätzlichen Schritt der Unterziehung besagter lyophylisierten Matrix einem dehydrothermalen Vernetzungsverfahren umfaßt.

21. Das Verfahren gemaß Anspruch 12, worin besagter Einlegeschritt des weiteren das Zumischen einer großen Anzahl an Glycosaminoglycan-Molekülen wie Chondroitin-4-sulfat, Chondroitin-6-sulfat, Keratansulfat, Dermatansulfat, Heparinsulfat, Hyaluronsäure und Gemischen davon umfaßt.

Revendications

1. Ménisque prothétique comprenant une matrice poreuse sèche de fibres biocompatibles et au moins partiellement biorésorbables,
   lesdites fibres comprenant des polymères naturels, par exemple le collagène, l'élastine, la réticuline, la cellulose ou leurs analogues ou leurs mélanges,
   ladite matrice étant conçue pour avoir in vivo un contour superficiel extérieur qui est essentiellement le même que celui d'un ménisque naturel, caractérisé en ce que
   ladite matrice a des dimensions des pores dans la gamme de plus de 50 µm à moins d'environ 500 µm,
   si bien que ladite matrice constitue un support au moins partiellement biorésorbable adapté à la croissance en profondeur des fibrochondrocytes méniscaux.

2. Ménisque prothétique selon la revendication 1, où ladite matrice a une forme essentiellement cunéiforme comprenant une large région centrale entre deux régions distales étroites d'extrémité.

3. Ménisque prothétique selon la revendication 1, où ladite matrice a une densité volumique d'environ 0,07 à 0,50 gramme de matrice par centimètre cube.

4. Ménisque prothétique selon la revendication 1, où ladite matrice a un espace intrafibrillaire et interfibrillaire d'environ 2 à 25 centimètres cubes par gramme de matrice.

5. Ménisque prothétique selon la revendication 1, où lesdits polymères naturels comprennent du collagène de type I et où lesdites fibres de collagène sont présentes à une concentration d'environ 75 à 100 % en poids sec, et lesdites molécules de glycosaminoglycanne sont présentes à une concentration d'environ 0 à 25 % en poids sec.

6. Ménisque prothétique selon la revendication 1, comprenant de plus plusieurs molécules de glycosaminoglycanne, par exemple du chondroïtine 4-sulfate, du chondroïtine 6-sulfate, du kératane sulfate, du dermatane sulfate, de l'héparine sulfate, de l'acide hyaluronique et leurs mélanges, entremêlées auxdites fibres, au moins une portion desdites molécules formant des réticulations entre certaines desdites fibres.

7. Ménisque prothétique selon la revendication 6, où lesdites fibres sont présentes à une concentration d'environ 75 à 100 % en poids sec et lesdites molécules de glycosaminoglycanne sont présentes à une concentration d'environ 0 à 25 % en poids sec.

8. Ménisque prothétique selon la revendication 1, où ladite matrice a la forme d'un coin à extension circonférentielle, par exemple d'un coin en forme de croissant, ayant une région centrale et une région périphérique et s'étendant selon un angle prédéterminé supérieur à 0 degré et inférieur ou égal à 360 degrés autour de ladite région centrale et
   où l'épaisseur dans ladite région centrale dudit coin est inférieure à l'épaisseur dans la région périphérique dudit coin.

9. Ménisque prothétique selon la revendication 1, comprenant de plus un treillis s'étendant à partir de portions de la surface extérieure de ladite matrice, ledit treillis étant résorbable et biocompatible.

10. Ménisque prothétique selon l'une quelconque des revendications 1 à 9 pour l'utilisation en thérapeutique, par exemple dans un procédé de régénération du tissu méniscal in vivo, comprenant les étapes de :
    (a) fabrication du ménisque prothétique selon l'une quelconque des revendications 1 à 9 et
    (b) implantation dudit ménisque prothétique dans une articulation du genou selon des techniques chirurgicales.

11. Ménisque prothétique selon la revendication 10, dans lequel ledit ménisque prothétique fabriqué dans l'étape (a) prend la forme d'un ménisque naturel lorsqu'il est implanté dans l'étape (b).

12. Procédé de fabrication d'un ménisque prothétique selon l'une quelconque des revendications 1 à 9 comprenant les étapes consistant à :
(a) placer plusieurs fibres biocompatibles et biorésorbables dans un moule, lesdites fibres comprenant des polymères naturels, par exemple le collagène, l'élastine, la réticuline, la cellulose ou leurs analogues ou mélanges, et ledit moule délimitant la forme d'une prothèse méniscale permettant la fonction articulaire du genou ;
(b) soumettre lesdites fibres à un premier et à un second cycles de congélation et de décongélation ;
(c) mettre lesdites fibres en contact avec un agent chimique réticulant, par exemple le glutaraldéhyde, le formaldéhyde, des aldéhydes biocompatibles et bifonctionnels, des carbodiimides, l'hexaméthylène diisocyanate, des bis-imidates, l'éther polyglycidylique du polyglycérol, le glyoxal et leurs mélanges, pour que lesdites fibres prennent la forme dudit moule ; et
(d) lyophiliser lesdites fibres réticulées.

13. Procédé selon la revendication 12, dans lequel ladite étape de mise en place comprend de plus la mise en place de plusieurs molécules de glycosaminoglycanne dans ledit moule.

14. Procédé selon la revendication 12, dans lequel ladite étape de mise en place comprend de plus l'étape d'orientation desdites fibres essentiellement circonférentiellement.

15. Procédé selon la revendication 14, dans lequel ladite étape d'orientation comprend la compression desdites fibres dans ledit moule avec un piston, où le mouvement du piston est essentiellement dirigé selon un axe de compression, tandis que, pendant ladite étape de compression, ledit piston tourne relativement audit moule autour dudit axe de compression.

16. Procédé selon la revendication 14, dans lequel ladite étape d'orientation comprend la rotation dudit moule lorsque lesdites fibres y sont placées.

17. Procédé selon la revendication 12, dans lequel ladite étape de mise en place comprend de plus l'étape d'orientation desdites fibres essentiellement radialement.

18. Procédé selon la revendication 12, comprenant de plus l'étape de compression desdites fibres avant ledit second cycle de congélation et décongélation.

19. Procédé selon la revendication 18, dans lequel ladite étape de compression comprend l'application d'une pression déterminée à une région de ladite matrice avec un piston, ledit piston ayant une forme prédéterminée.

20. Procédé selon la revendication 18, comprenant de plus l'étape additionnelle consistant à soumettre ladite matrice lyophilisée à une opération de réticulation déshydrothermique.

21. Procédé selon la revendication 12, dans lequel ladite étape de mise en place comprend de plus l'entremêlement de plusieurs molécules de glycosaminoglycanne tel que le chondroïtine 4-sulfate, le chondroïtine 6-sulfate, le kératine sulfate, le dermatane sulfate l'héparine sulfate, l'acide hyaluronique et leurs mélanges.

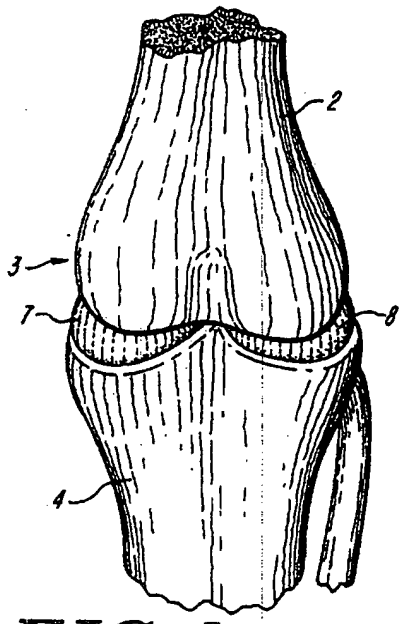
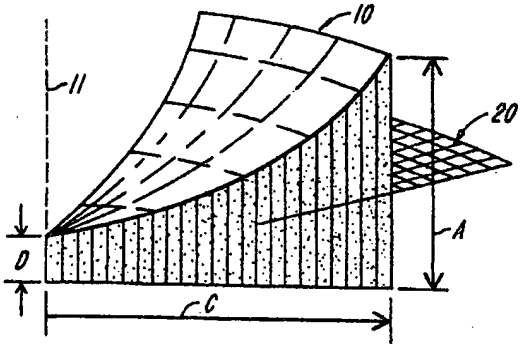


FIG. 1

FIG. 3



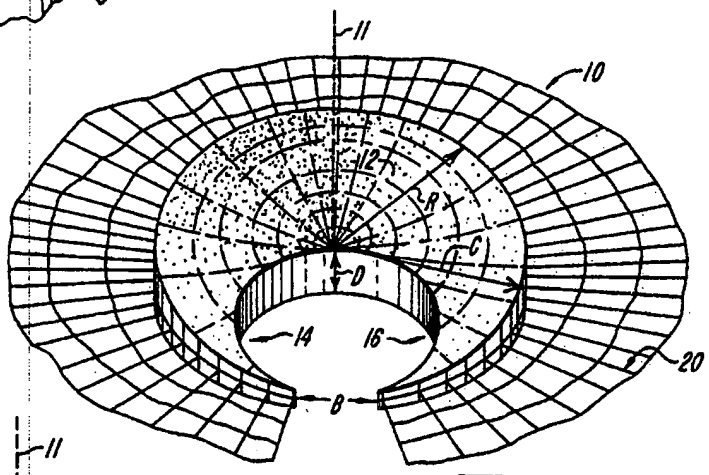


FIG. 2

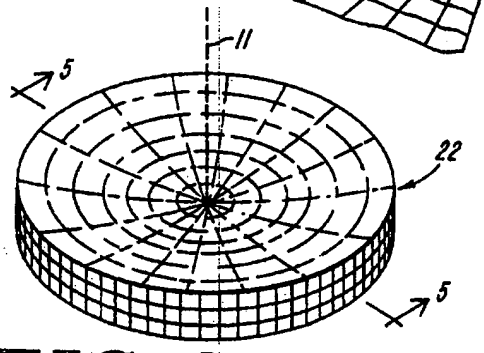
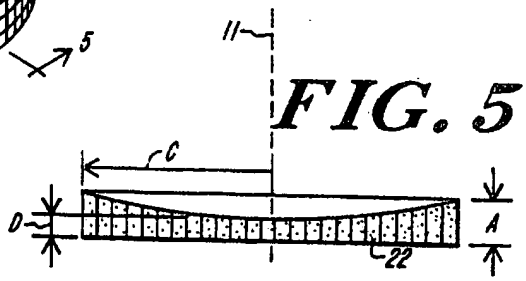


FIG. 4

FIG. 5



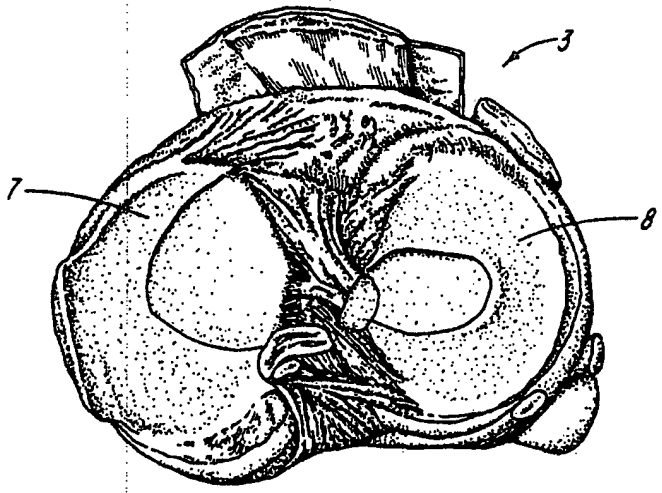


FIG. 1A

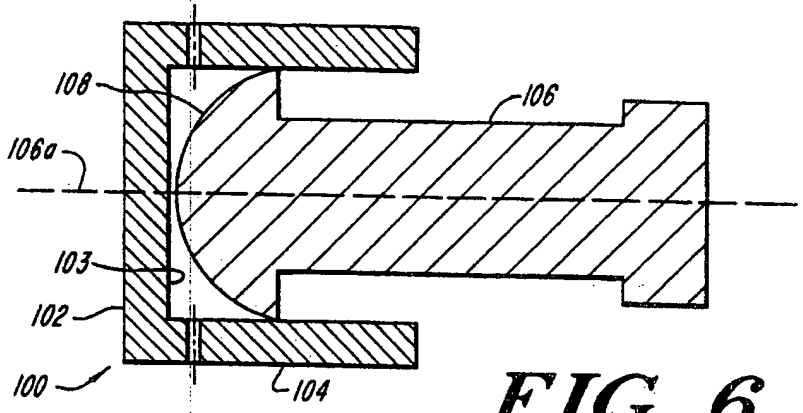


FIG. 6

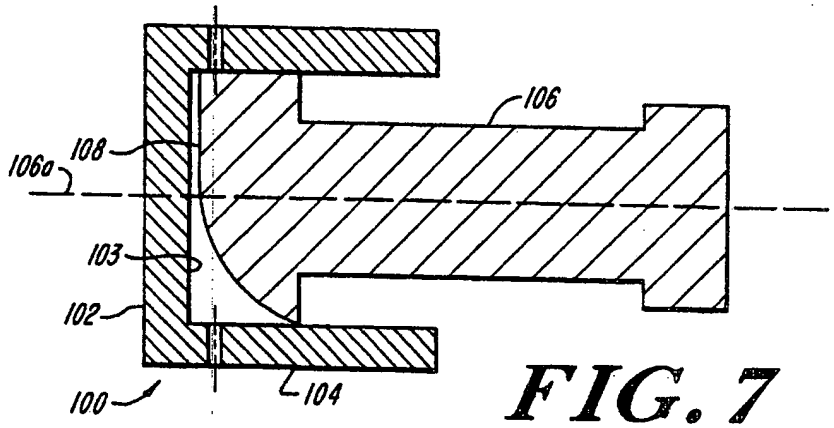


FIG. 7

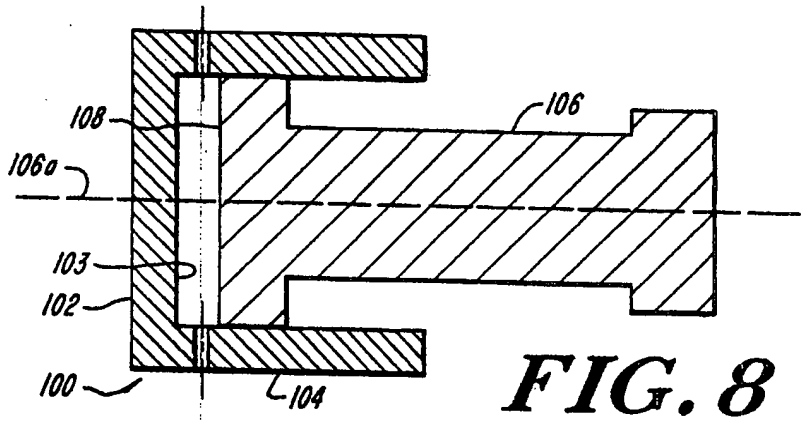


FIG. 8

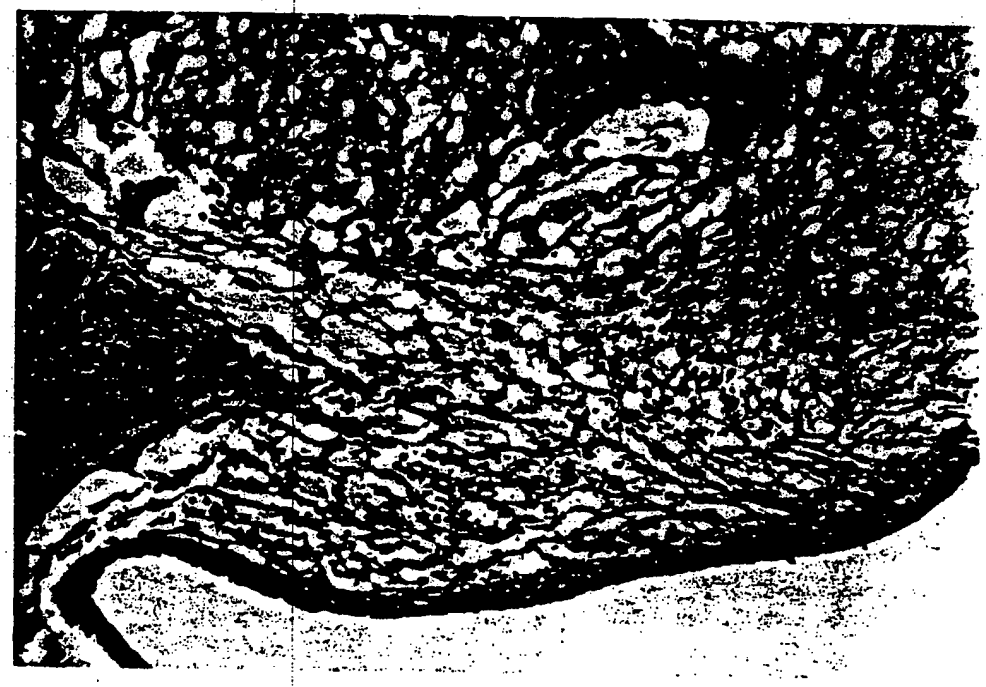


FIG. 9

FIG. 10

FIG. 11

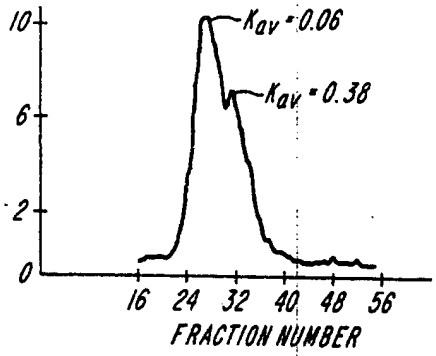


FIG. 12A

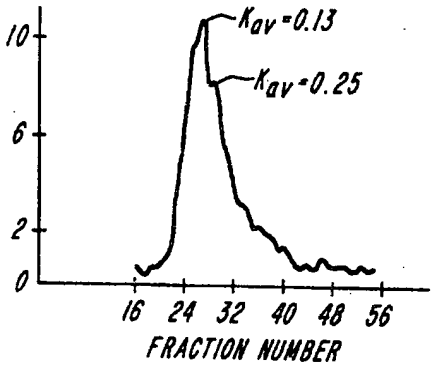


FIG. 12B

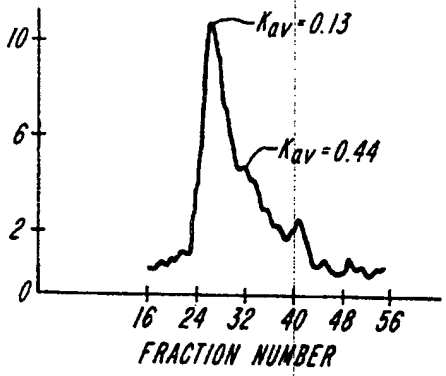


FIG. 12C

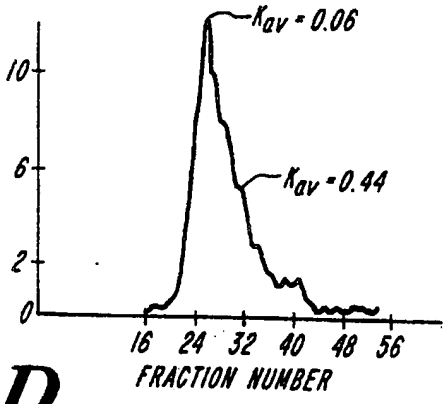


FIG. 12D

This Page is Inserted by IFW Indexing and Scanning Operations and is not part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☑ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☑ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☑ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.
As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.